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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/034,950	12/26/2001	Bhami Shenoy	VPI/00-08	9344

1473 7590 02/12/2008

ROPES & GRAY LLP
PATENT DOCKETING 39/361
1211 AVENUE OF THE AMERICAS
NEW YORK, NY 10036-8704

EXAMINER	
KIM, ALEXANDER D	
ART UNIT	**PAPER NUMBER**
1656	

MAIL DATE	DELIVERY MODE
02/12/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/034,950	SHENOY ET AL.	
	Examiner	Art Unit	
	Alexander D. Kim	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 August 2007 and 01 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *84-94* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *84-94* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/17/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Notice to Comply*.

DETAILED ACTION

Application Status

Continued Examination Under 37 CFR 1.114

1. The art unit location of your application and/or examiner has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1656, Examiner Alexander Kim.

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 27, 2007 has been entered.

Applicants' amendment canceling Claims 1-83; amending Claim 85 in the paper of August 27, 2007 is acknowledged. Thus, Claims 84-94 are pending in the instant Office action.

Information Disclosure Statement

3. The information disclosure statement (IDS) filed on 12/17/2007 has been reviewed, and its references have been considered as shown by the Examiner's initials next to each citation on the attached copy.

Compliance with Sequence Rules

4. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to fully comply with the requirements of 37 C.F.R. 1.821 through 1.825; Applicants' attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990).

Six amino acid sequences listed under "N-terminal sequence" on page 108 require appropriate SEQ ID NOs. Appropriate correction is required.

If the noted sequences are in the sequence listing as filed, Applicants must amend the specification to identify the sequences appropriately by SEQ ID NO. If the noted sequences are not in the sequence listing as filed, Applicants must provide (1) a substitute copy of the sequence listing in both computer readable form (CRF) and paper copy, (2) an amendment directing its entry into the specification, (3) a statement that the content of the paper and CRF copies are the same and, where applicable, include no new matter as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.821(b) or 1.825(d), and (4) any amendment to the specification to identify the sequences appropriately by SEQ ID NO.

Claim Objections

5. Claims 91 and 94 are objected to in the recitation of "any one of claims 86 to 90 and 92 to 93" in claim 91 and "any one of claims 86-89 or 92-93" in claim 94, in the

recitation of "any one of claims 86 to 90 and 92 to 93" in claim 91 and "any one of claims 86-89 or 92-93" in claim 94. In order to improve claim form, the Examiner suggests replacing "and" with "or" in Claim 91 to recite "any one of claims 86 to 90 or 92 to 93" and in claim 94 to recite "any one of claims 86-89 or 92-93".

Objections to the Specification

6. The specification is objected to because the abstract of the disclosure filed on 3/25/2002: (a) is not on a separate page in accordance with 37 CFR 1.52(b)(4); (b) has more than one paragraph; and (c) has more than 25 lines/250 worlds. See MPEP § 608.01(b) for more detail. A new abstract of the disclosure is required and must be presented on a separate sheet, apart from any other text.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 86-94 are rejected under of 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(a) Claims 86 (Claims 87-91 and 94 dependent therefrom), 92 and 93 recite the limitation "crystal of good quality and yield". However, the term “good quality” or “good…yield” is relative term, which renders the claim indefinite. It is unclear what

criteria (or a point of reference) is intended as being used to determine if a crystal has a good quality and good yield. Appropriate clarification is required.

(b) Claims 86 (Claims 87-91, 94 dependent therefrom), 92 and 93 recite the limitation "the crystallization buffer that characterized" referring to the crystallization buffer that is characterized from (or by) the selected micro-batch crystallization solution for scaling up a process. This rejection is based on the lack of clarity regarding the term "characterized", because it is unclear as to the intended buffer that “characterized the selected microbatch crystallization solution”. Is this term intended to refer back to the solution with the buffer that “produces antibody crystals of good quality and yield” or to some other buffer? It is suggested that applicant clarify the meaning of the noted phrase.

Claim Rejections - 35 USC § 112 – 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 84, 85, 91 and 94 are rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejection was stated in the previous office action as it applied to previous Claims 84, 85 and 94. See particularly paragraphs 7 and 12 of the Office action filed on 2/26/07. In response to this rejection, applicants have amended Claim 85 and traverse the rejection as it applies to the newly amended claim(s). Upon further consideration, claim 91 is included in the instant rejection for reasons that follow.

Applicants argue that the Examiner refuses to accept four actual examples (Infliximab) and several other examples, which is in possession of the claimed invention and these specific examples lay to rest those general concerns about lacking adequate written description (see page 10, Remarks). Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons.

However, four actual examples (Infliximab) and several other examples do not sufficiently represent the claimed genus of crystals (i.e., any infliximab crystals in Claim 84; a composition of any whole antibody crystals in a Claims 85 and 94; and any antibody crystal in Claim 91), which one skilled in the art clearly would not be in possession of the claimed genus of crystals by the instant disclosure. As noted in the previous office action, "simply selecting" the appropriate buffer is difficult enough for crystallization of a protein or antibody. Which one will work for all antibody crystals? It clearly is a diverse combination as demonstrated by all of Applicants' examples, and it is not just one buffer which will work. It is a mixture of salt, pH, temperature, solvents, additives, buffer choice, protein concentration, etc. So which one, or which combinations do Applicants suggest will work for all antibody crystals? The art clearly suggests that it is not just one and McPherson et al. suggest it is a combination of 25

different parameters, not simply one. Furthermore, the scope of the Applicants claims (84 and 94) does encompass every single Infliximab crystal derivative, homolog or variant thereof, every Fab, Fab2, single chain antibody, etc., for batch crystallization and/or structural determination. Likewise, claim 85 for the whole antibody crystals of every single potential and conceivable kind of antibody, from any source, derivatized in any manner (e.g. chimeric, humanized, covalently corsslinked with any molecules etc.) wherein said antibody concentration is greater than 50 mg/ml. In order for a broad generic claim to satisfy the written description requirement, the specification must provide adequate description in the specification to reflect the variation in the genus by describing a sufficient number of representative species. In Regents of the University of California v. Eli Lilly & Co. the court stated:

> "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Fiers, 984 F.2d at 1171, 25 USPQ2d 1601; In re Smythe, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus ...") Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

Thus, the species which are described in the specification are not deemed to be representative of the entire genus of antibody crystals for which the claims are drawn to because these representative species fail to reflect the wide variation among the members of the genus. For the reasons above and reasons stated in the previous

office actions, the Claims 84, 85, 91 and 94 stand rejected under 35 USC 112, first paragraph, for written description.

9. Claim(s) 84, 85, 91 and 94 are rejected under 35 U.S.C. 112, first paragraph, scope of enablement, because the specification, while being enabling for antibody crystals of RituxanTM, RemicadeTM or HerceptinTM (assuming the structures of these brand name antibodies has not been modified over time) as shown in the Examples 1-28, 33-37 and 31-33; does not reasonably provide enablement for all crystals as broadly encompassed by the claims.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The rejection was stated in the previous office action as it applied to previous Claims 84, 85 and 91. See particularly paragraphs 4 and 9 of the Office action filed on 2/26/07. In response to this rejection, applicants have amended Claims 85 and traverse the rejection as it applies to the newly amended claim(s). Upon further consideration, claim 94 is included in the instant rejection for reasons that follow.

Applicants argue that the applicants provide four different examples of making Infliximab crystals and crystals of various other whole antibodies (Claim 85) should be more than enough to satisfy the enablement requirement.

Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons. The four working examples are not enough to

satisfy the enablement requirement, particularly in view of the broad scope of the claims, the high level of unpredictability, the lack of guidance and working examples, and the amount of experiment. The disclosed working examples are not commensurate with the broad scope of the claims and in view of the detailed analysis of the factors of In re Wands as set forth in prior office action, the specification fails to fully enable crystals as encompassed by the claims.

As noted in the previous office action, while the disclosure of a single method of making a product does enable some products, in arts where the unpredictability is so great, more than one example may be required. Furthermore, in the case of protein crystallography, the art of making any crystal is so extremely unpredictable that the disclosure of four ways to make said Infliximab crystal is not considered to be adequate because the scope of the claims encompasses numerous Infliximab crystals (in claims 84 and 94), or any whole antibody crystal (claim 85 and 91). As stated, in applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. In re Soll, 97 F.2d 623, 624, 38 USPQ 189, 191 (CCPA 1938). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); In re Vaeck, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one or a few species,

what other species will work. Likewise, it is not obvious from the disclosure if the same processes would work for Fab, Fab2, or other variants of any Infliximab crystal and it is clear from the prior art that what works for one 'native' crystal may not work for another. Likewise the scope of claim 85 for any whole antibody crystal, or any antibody in claim 91, from any species or source, or any whole antibody variant (e.g. chimeric or humanized), encompasses so many different species whereas only a few examples exist in art of extreme unpredictability. Thus, the conclusion is that the claims exceed the scope of enabling disclosure and one skilled in the art would not be able to make and use the full scope of claimed antibody crystals by the instant teaching with out undue experimentation.

10. Claim(s) 86-94 are rejected under 35 U.S.C. 112, first paragraph, scope of enablement, because the specification, while being enabling for a method of crystallizing antibody crystals of RituxanTM, RemicadeTM or HerceptinTM (assuming the structures of these brand named antibody has not been modified over time) by the Examples 1-28, 33-37 and 31-33; does not reasonably provide enablement for all (large or small) crystallization method as broadly encompassed by the claims.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The rejection was stated in the previous office action as it applied to previous Claims 86-94. See particularly paragraphs 5 and 10 of the Office action filed on 2/26/07.

In response to this rejection, applicants have amended Claims 85 and traverse the rejection as it applies to the newly amended claim(s).

Applicants argue that the applicants providing four different examples of making Infliximab crystals and crystals of various other whole antibodies (Claim 85) should be more than enough to satisfy the enablement requirement. Applicants argue that the applicants providing four different examples of making Infliximab crystals and crystals of various other whole antibodies (Claim 85) should be more than enough to satisfy the enablement requirement. Applicants also argue that "the claimed method works for two antibodies and says that it works for nine others" (see middle of page 9, Remarks). Applicants also argue that the examiner ignores the specific teachings of applicants' disclosure and points to nothing but general crystallization concerns.

Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons. The four examples is not enough to satisfy the scope of enablement requirement when the undue experimentation is required as described in the previous office actions because claimed method of crystallization is overly broad. The represented species by the example do not commensurate with the claimed scope and failed to satisfy the scope of enablement requirement. Applicants recites that the exemplified conditions "works for nine others", which is not entirely true in view of instant specification reciting "the crystallization conditions exemplified above are useful for the crystallization" along with the list of nine antibody. Said conditions are useful but did not explicitly state that these conditions resulted in the formation of crystal except one (i.e., HerceptinTM in view of Figures 11 and 14). Also, it is noted that general

concern of crystallization governs the enablement of antibody crystal because an antibody comprises amino acid sequences. One skilled in the art knows the crystallization of antibody is not excluded from the generality of any protein crystallization. Because the claimed antibody crystal encompass very widely varying structure, including crystallization of any fragment, or with/without any crosslinking agent, which further modifies the antibody; the instant disclosure do not enable one skilled in the art to make and use the full scope of claimed antibody crystal(s). It is noted, the method of the Example of 32 and 33 in the instant specification are identical.

As disclosed in the previous office action, there is no dispute that Applicants have taught how to crystallize two antibodies in a large-scale batch method based upon the micro-batch conditions. However, the leap between asserting that this therefore teaches how to successfully produce antibody crystals for all antibodies in the same manner is more than the prior art teaches is reasonable to expect. Applicants suggest that the Examiner cannot rely only on the unpredictability factor. However, in protein crystallization methods, there is clearly no escaping this factor. Furthermore, unpredictability is not the only factor outlined by the Examiner, it is one of eight factors (Wands factors) that culminate in the conclusion that the claims are not enabled for the entire scope. As was outlined in the previous Office action, the Wands factors of (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims all were

taken into consideration. The conclusion is and was that the quantity of experimentation necessary to practice the entire scope of the claimed subject matter is enormous (1) because finding successful micro-batch crystallization conditions in the first place is extremely difficult and unpredictable in the science which is then further complicated and compounded by the fact that it is not exactly straight forward to leap from micro-batch conditions to large scale production; (2 and 3) the amount of direction in the specification provides for two examples which may or may not work for other antibodies, (4) the nature of the invention is that crystallization of anything at all is extremely difficult and difficult, (5-8) the nature of the prior art suggests crystallizing anything is nothing but trial-and-error, even today with all of the advances in technology and automated robotic assistance, there is nothing predictable or easy about crystallizations. In fact, it is very well known in the art that luck often times is one of the main factors in facilitating successful crystallizations. Cudney et al. (see "Protein Crystallization and Dumb Luck", entire article, The Rigaku Journal. 1999. Vol. 16, No. 1, pp. 1-7.) describe the role of luck in many different crystallization experiments in his own lab and acknowledge that nearly every single crystallographer in existence has similar stories of fortuitous crystal growth and that they do not, however, publish these "findings" for fear of looking foolish. Furthermore, large scale production of therapeutic proteins are very well known, insulin (see US 4,959,351 and 6,310,038) and human growth hormone (see US 5,780,599) are just two of the many therapeutic protein crystals which have been scaled up for production of large scaled production using very similar methods that Applicants are claiming. However, what makes the instant

invention and others like it non-obvious is the crystallization of specific proteins or antibodies that have been successfully produced and is non-obvious because of the fact that what does work for one protein or antibody will not necessarily work for another, even if you have starting conditions to begin with. Furthermore, in claims 86, 92 and 93, what guidance in the specification is there for "preparing a series of different micro-batch crystallization solutions each of a total volume of at least 33/75/100 □l wherein each solution comprises the antibody and different crystallization buffer" other than the specific examples for specific antibodies. The crystallization buffer works for each different antibody will be different and a grand assertion that the conditions taught by Applicants will work for all antibodies on a microscale goes against the teachings of the prior art. For instance, even if you had the conditions to successfully produce whole antibody crystals, the same conditions are likely completely different for any derivative thereof, e.g. Fab, Fab2, single change Fv, etc. because the prior art teaches for example, that there 25 different parameters which do or could affect crystallization of each protein/antibody (see McPherson (Eur. J. Biochem. 1990, 189:1-23), Table 2, p. 13) and that each protein is assessed on its own biophysical characteristics. It is stated (p. 13, 2nd column, Factors influencing protein crystal growth):

> "Table 2 lists physical, chemical and biological variables that may influence to a greater or lesser extent the crystallization of proteins. The difficulty in properly arriving at a just assignment of importance for each factor is substantial for several reasons. Every protein is different in its properties and, surprisingly perhaps, this applies even to proteins that differ by no more than one or just a few amino acids. There are even cases where the identical protein prepared by difference procedures or at different times may show significant variations. In addition, each factor may differ considerably in importance for individual proteins."

Furthermore, even though the skill in the art is extremely high, even for those that are graced by being assisted with the latest technologies such as automated robotics, the art of crystallography is still rooted in trial-and-error procedures (see Abstract, Kundrot et al. Cell. Mol. Life Sci. 2004, 61: 525-536) and currently there are no directed methods which makes this process any easier or more predictable. Thus, each protein or antibody that is to be crystallized needs to be treated as its own entity possessing its own unique biochemical crystallization parameters which cannot be inferred or learned from other crystallized proteins.

For these reasons, the breadth of the claims exceed that which is enabled by the specification. And for these reasons lack of enablement is considered proper and one skilled in the art would not be able to make and use the full scope of claimed antibody crystals by the instant teaching with out undue experimentation.

11. Claim(s) 86-94 are rejected under 35 U.S.C. 112, first paragraph, scope of enablement, because the specification, while being enabling for a method of crystallizing antibody crystals of RituxanTM, RemicadeTM or HerceptinTM (assuming the structures of these brand named antibody has not been modified over time) by the Examples 1-28, 33-37 and 31-33 which are "micro-batch crystallization" method; does not reasonably provide enablement for all "large-batch crystallization method" as broadly encompassed by the claims.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The rejection was stated in the previous office action as it applied to previous Claims 90, 91, and 94. See particularly paragraph 11 of the Office action filed on 2/26/2007. In response to this rejection, applicants have amended Claims 85 and traverse the rejection as it applies to the newly amended claim(s). Claims 86-89 and 92-93 were not included in the previous rejection, scope of enablement. However, upon further consideration, claims 86-89 and 92-93 are included in the instant rejection for reasons explained below.

Applicants argue that the Examiner has ignored applicants' specific disclosures and relies on general concern about a method of crystallization; thus, instant rejection should be withdrawn.

Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons. The four micro-scale crystallization in the example is not enough to satisfy the scope of enablement requirement when the undue experimentation is required as described in the previous office actions because claimed "large-batch crystallization" is overly broad. The represented species by the example do not commensurate with the claimed scope and failed to satisfy the scope of enablement requirement.

As noted in the previous office action, the Examiner can find no disclosure in the specification where Infliximab crystals have been produced by the large batch methods

as stated in the response. Every example of crystallization of Infliximab was performed on the microscale level and not translated or scaled-up to the large scale method. Furthermore, the assertion that the Examiner has provided no reason why these buffers would not produce Infliximab crystals is erroneous. The prior art points to the fact suggests otherwise and is what was stated in the previous Office action. Jen et al. (Pharm. Res. 2001, 18(11):1483-148), teach an overview of the success over the years of producing protein crystals on a large scale for the use in pharmaceuticals, specifically state the following (p.1487, 1st column, 2nd paragraph):

> "Once a crystal candidate has shown promising properties for pharmaceutical development, the crystallization effort must be up-scaled. The batch and dialysis methods are likely the easiest options for adaptation to large-scale crystallization because similar constructions already exist for chemical, pharmaceutical, and biotechnological processes. *The conversion of microliter-size crystallization trials into industrial dimensions, however, may be a challenging task*."

Applicants seem to completely dismiss what the prior art teaches and that the predictability in going from the small to large scale is not a trivial matter which will work consistently for every single antibody and that each antibody needs be taken on a case by case basis.

As further evidence of the problems of scaling from small scale to large is given by Klyushnichenko (Curr. Op. Drug Discovery, 2003, 6(6):848-54) wherein the following is taught (p. 849, 1st column, 2nd paragraph):

> The objectives of a bulk protein crystallized process are to rapidly purify and concentrate the produce with high yield and without loss in potency. However, crystallization has not been used widely in the purification or formulation of biological compounds. *This is due to the difficulties in developing crystallization conditions that are reproducible and scalable at clinical- and commercial-scale*."

Klyushnichenko does give several examples where successful conversion from microscale to large scale crystallization has been achieved, most notably in insulin formulations. However it is also taught:

> As discussed above, there are several examples of large-scale protein crystallization; however, researchers frequently report that no clear understanding of the protein crystallization mechanism has yet emerged. Typically several hundred experiments must be performed to determine crystallization conditions, such as pH, buffer type, precipitant type and protein concentration. To control costs and improve efficiency, it is important to minimize the number of experiments, especially if the final or intermediate conditions are to be scaled-up.

The enablement requirement clearly delineates the predictability in the art and correlates this with the amount information necessary in the specification. If little is known in the prior art about the nature of the invention and the art is unpredictable, the specification needs more detail as to how to make and use the invention in order to be enabling. In the instant case, however, the nature of the invention and the prior art readily acknowledges the challenges and unpredictability in the art. The "predictability or lack thereof" in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there is lack of predictability in the art. Accordingly, what is known in the art provides evidence as to the question of predictability. In

particular, the court in In re Marzocchi, 439 F.2d 220, 223-24, 169 USPQ 367, 369-70 (CCPA 1971), stated:

> "[I]n the field of chemistry generally, there may be times when the well-known unpredictability of chemical reactions will alone be enough to create a reasonable doubt as to the accuracy of a particular broad statement put forward as enabling support for a claim. This will especially be the case where the statement is, on its face, contrary to generally accepted scientific principles. Most often, additional factors, such as the teachings in pertinent references, will be available to substantiate any doubts that the asserted scope of objective enablement is in fact commensurate with the scope of protection sought and to support any demands based thereon for proof. [Footnote omitted.]"

In the instant case, what is known in the art and the required undue experimentation imposed upon one skilled in the art because the breadth of the claims exceed that which is sufficiently supported in the specification and is supportive of the lack of enablement to make and use the full cope of claimed method of "large-batch crystallization".

Claim Rejections - 35 USC § 102/103

13. Claim 85 is rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Ely et al. (Biochemistry, 1978, 17(5):820-23) as evidenced by Chayen (2004, Current Opinion in Structural Biology, 2004, 14: 577-583). See MPEP 2112.III regarding a rejection under 35 U.S.C. 102/103. See also MPEP 2131.01 regarding a multiple reference 35 U.S.C. 102 rejection and MPEP 2124 noting the critical date of extrinsic evidence showing a universal fact need not antedate the filing date.

The claim is drawn to a pharmaceutical composition comprising a whole

antibody crystal wherein the concentration of said antibody is greater than 50 mg/ml. The claim has been construed in accordance with MPEP 2111 as meaning that the antibody of the crystal has a concentration greater than 50 mg/mL.

Ely et al. teach crystallization of the whole antibody of human IgG2 wherein the antibody concentration prior to crystallization is 20-22 mg/ml. Ely et al. teaches crystallization of the antibody by microdiffusion against 0.1M borate, 0.05M NaCl at pH 7.0 (see p. 820,.2nd column, last line to p. 821, 1st column, first line). Thus the crystal forms in a pharmaceutically acceptable buffer and is thus considered to be in a pharmaceutical composition.

As noted above, claim 85 recites “a whole antibody crystal wherein said antibody concentration is greater than 50 mg/ml", which has been broadly, but reasonably interpreted as meaning that the antibody in crystal form has a concentration greater than 50 mg/ml. While it is acknowledged that the concentration of the antibody of Ely et al. *prior to* crystallization is 20-22 mg/mL, it is noted that in the process of crystallizing the antibody according to Ely et al., the loss of water due to precipitation necessarily increases the protein concentration as evidenced by the phase diagram in Figure 1 on page 579 of the reference of Chayen et al. According to Figure 1 of Chayen et al, the concentration of protein is increased in a crystal compared to protein concentration in solution. Thus crystallization of the antibody at a concentration of 20-22 mg/mL would appear to necessarily result in a crystalline antibody at a concentration greater than 50 mg/mL.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

13. Claims 84, 85, 91 and 94 are rejected on the ground of nonstatutory double patenting over claims 2-15, 20, 27, 31, 33-35, and 41 of U. S. Patent Application No. 10/741,861 since the claims, if allowed, would improperly extend the "right to exclude" already granted in the patent.

The subject matter claimed in the instant application is fully disclosed in the US patent application and the application are claiming common subject matter, as follows: Instant claims 84, 85, 91 and 94 overlap the scope of disclosed in claims of 3 (Claims 4-15, 20, 27, 31, 33-35, 41 dependent therefrom) and/or 35, from US Patent Application No. 10/741,861, which discloses a spherical protein particle wherein said protein is an

antibody (or Infliximab in Claim 35) wherein said particle is produced by the slow addition of a crystallizing/precipitating agent.

Claim 2 (Claim 4-15, 20, 41 dependent therefrom) of US Patent Application No. 10/741,861 is also drawn to the spherical protein particle wherein said spherical protein particle is a spherical nanocrystalline composite particle, which encompasses any antibody crystal of instant claims 91 sand 94. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alexander D. Kim whose telephone number is (571) 272-5266. The examiner can normally be reached on 11AM-7:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on (571) 272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you

have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Alexander D Kim/

Examiner, Art Unit 1656

/David J. Steadman/

Primary Examiner, Art Unit 1656